BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

PATENT SPECIFICATION

(11) 1 292 785

BB

1292785

NO DRAWINGS

(21) Application No. 22811/71 (22) Filed 19 April 1971

(31) Convention Application No. 31143 (32) Filed 17 Oct. 1970 in

(33) Italy (IT)

(45) Complete Specification published 11 Oct. 1972

(51) International Classification C07C 169/36 169/24

ERRATUM

SPECIFICATION No. 1,292,785

Page 1, Heading, (72) Inventors *for* PIFFER
read PIFFERI

THE PATENT OFFICE
16th February, 1973

PATENTS ACT 1949

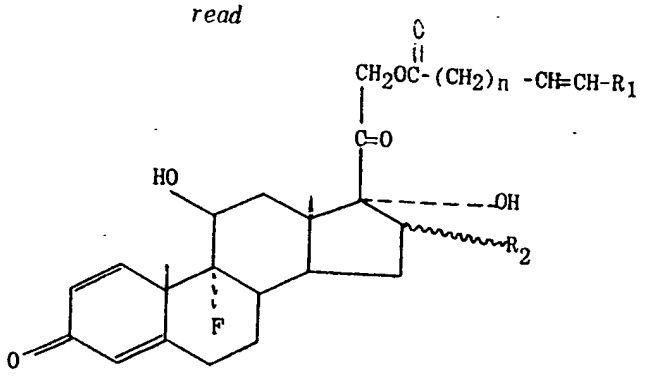
SPECIFICATION NO 1292785

SLIP No. 2

The following corrections were allowed under Section 76 on 4 July 1975

Page 1, line 21
Page 4, line 32
} *for* existing formula

read



THE PATENT OFFICE
4 August 1975

R 23948/1

or a group of the formula

30

$$-CH_2-CH=CH-CH_2-CH=CH-CH_2-CH_3.$$

30

SEE ERRATA SLIP ATTACHED

PATENT SPECIFICATION (11) 1292785

1292785

NO DRAWINGS

(21) Application No. 22811/71 (22) Filed 19 April 1971

(31) Convention Application No. 31143 (32) Filed 17 Oct. 1970 in

(33) Italy (IT)

(45) Complete Specification published 11 Oct. 1972

(51) International Classification C07C 169/36 169/34

(52) Index at acceptance

C2U 2 4A2 4B2 4C4 4C5 4X 5

(72) Inventors GIORGIO PIFFER and MARIO PINZA

(54) DERIVATIVES OF DEXA- AND BETA-METHASONE, THEIR PRODUCTION AND USE

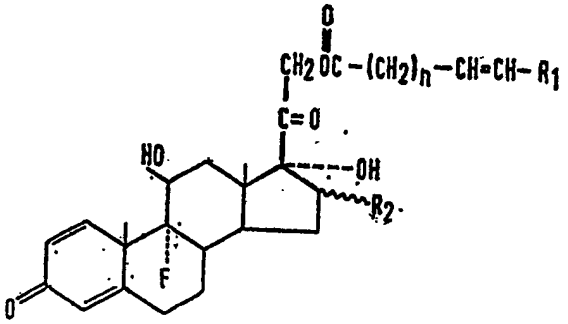
(71) We, I.S.F. S.p.A., an Italian Body Corporate of Via Calatafimi 5—9, Milan, Italy, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The invention relates to novel pregnene compounds, to a method for their preparation and also to their pharmaceutical use. In accordance with the invention the novel compounds are produced by esterifying the alcoholic group in the 21-position of a corticoid with an unsaturated higher fatty acid having non-cumulative double bonds. The novel compounds of the invention have high antiphlogistic, (i.e. anti-inflammatory) anti-exudative and antipruritic activities.

It is known that the antiphlogistic activity of a corticoid is substantially affected by the kind of acid radical bonded to the 21-position; furthermore, the lipophilic character of a steroid is enhanced by aliphatic high-molecular weight chains in the 21-position.

It has now been found that the esters of the high molecular weight aliphatic chains obtained by esterifying the alcoholic group of the 21-position in the steroid nucleus with certain unsaturated carboxylic acids, for instance, oleic acid, linoleic acid or arachidonic acid show new and unexpected features.

According to the invention, there are provided pregnene compounds of the general formula:



wherein R_1 is an unsaturated or saturated aliphatic hydrocarbon group having from 8 to 14 carbon atoms, for instance, either 8 carbon atoms or 14 carbon atoms, R_2 is an α-orientated or β-orientated methyl group, and n is a positive integer of from 3 to 7, preferably either 3 or 7.

When n has a value of 7, the substituent R_1 is preferably an n-octyl group, a group of the formula

$$-CH_2-CH=CH-(CH_2)_4-CH_3$$

or a group of the formula

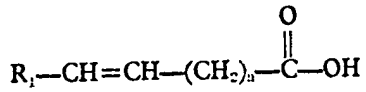
$$-CH_2-CH=CH-CH_2-CH=CH-CH_2-CH_3.$$

In the case where n has a value of 3, the substituent R_1 is preferably a group of the formula

$$-(CH_2CH=CH)_3(CH_2)_4CH_3.$$

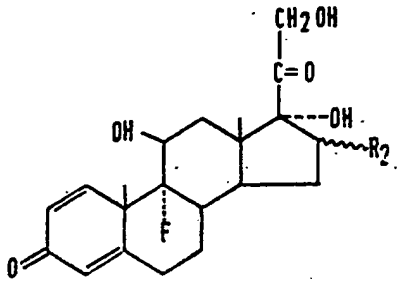
The esters of the invention may be prepared by a process comprising reacting an unsaturated fatty acid or salt thereof (usually about an equimolar amount), the said fatty acid having the formula:

(II)



wherein R_1 and n are as defined above, with dexa-methasone or beta-methasone or a 21-ester thereof, the aforesaid methasone having the formula:

(III)



wherein R_2 is as defined above.

The unsaturated fatty acid of the general formula (II) is preferably linoleic acid, oleic acid, arachidonic acid or linolenic acid. The methasone may be in the form of the 21-mesylate.

The reaction is conveniently carried out in an aprotic solvent for example, dimethyl formamide, and is preferably effected at a temperature of 10°C. to 70°C. especially 50°C. In order to avoid oxidation of the double bonds in the unsaturated fatty acid, the reaction should preferably be carried out in an inert atmosphere (e.g. nitrogen).

The esters of the invention are oily or soft fatty materials, whereas the esters prepared from saturated acids having the same number of carbon atoms (e.g. palmitic acid) are crystalline solids. This feature may have desirable effects on both the surface penetration and the extension in time ("delay effect") of the drug. A surface penetration may occur in the absence of the usual carriers although the latter are usually desirably present, mostly for facilitating the administration of the drug.

In connection with the "delay effect" referred to above, it has been found that the cortisone-related moiety of the esters according to the invention is slowly and gradually released by hydrolysis of the ester bond, thereby permitting distribution and extension of the therapeutical action over a suitable period of time. The above features, in conjunction with the absence of side-effects, which results from the lack of systematic action, render the esters according to the invention to show a relatively high topical anti-phlogistic action.

The esters of this invention may, for their therapeutic function, be administered alone or in admixture with inert and pharmaceutically acceptable diluents or carriers and/or other biologically active compounds.

Embodiments of the invention will now be described by way of example in the following Examples:

Example 1:

9α-fluoro-11β,17,21-trihydroxy-16α-methyl-pregna-1,4-diene-3,20-dione 21-octadec-cis-9-enoate (Dexamethasone 21-oleate)

To a stirred solution of 9α-fluoro-11β,17,21-trihydroxy-16α-methyl-pregna-1,4-diene-3,20-dione (10 g.; 25.5 millimoles) in 20 ml. pyridine and 12 ml. acetone at −10°C. a cold solution of methane sulfonyl chloride (3 ml.; 38.5 millimoles) in 8 ml. acetone was added dropwise. The addition was completed within about 3 hours, and

the mixture was then left standing in the cold for a further 1.5 hours after which 200 ml. cold water were added. The resulting precipitate as separated by filtration and washed with water to give 11.5 g. (96% of theoretical yield) of dexamethasone 21-mesylate, m.p. 208—210°C. (dec.).

The above mesylate (intermediate) was added, in a nitrogen atmosphere, to a stirred slurry of potassium octadec-cis-9-enoate (7.85 g.; 24.5 millimoles) in 70 ml. dimethyl formamide (DMF). After stirring for 1.5 hours at 50°C. and evaporating the DMF in vacuo at the same temperature, the residue as washed by slurrying it into water and then was redissolved in methylene chloride, dried and the solvent evaporated. The residue was purified by chromatography on an inactivated (10% water) silica gel column (550 g.), by using an ethyl acetate/hexane mixture (7:3) to give a very good yield of an oil which forms a unitary spot at $R_f=0.65$ in a thin layer chromatographic analysis carried out with the same eluent.

Chemical-physical characteristics: $[\alpha]_D^{20}=+84.9°$ (C=1% in $CHCl_3$); λ_{max}(MeOH)=240 mμ (ε=14.100); IR (*nujol) cm^{-1}: 3470 (11 O—H and 17 O—H), 1735—1715 (C=O ester and 20-keto), 1660, 1620, 890 (C=O 3-keto $\Delta^{1,4}$); NMR ($CDCl_3$) δ: 4.93 (s, 2H, C—21 CH_2), 5.10—5.65 (m, 2H, olefinic protons in chain), 6.10 (d, $J_{2,4}=1$ cps, 1H, C—4 C—H), 6.32 (dd, $J_{2,4}=1$ cps, $J_{1,2}=10$ cps, 1H, C—2 C—H), 7.24 (d, $J_{1,2}=10$ cps, 1H, C—1 C—H). (* "Nujol" is a Registered Trade Mark).

The results of the analysis are in accordance with empirical formula $C_{40}H_{61}FO_6$.

Example 2:

9α-fluoro-11β,17,21-trihydroxy-16α-methyl-pregna-1,4-diene-3,20-dione 21-octadeca-cis-9, cis-12-dienoate (Dexamethasone 21-linoleate)

The dexamethasone 21-mesylate (11.5 g.; 24.5 millimoles) prepared as described in Example 1 was added in a nitrogen atmosphere to a stirred slurry of potassium actadeca-cis-9, cis, 12-dienoate (7.81 g.; 24.5 millimoles) in 70 ml. DMF. After stirring for 1.5 hours at 50°C. and evaporating the solvent *in vacuo* at the same temperature, the residue was washed by slurrying it into water and was then redissolved in methylene chloride, dried and the solvent evaporated. The residue was purified by chromatography on an inactivated (10% water) silica gel column (470 g.) by using an ethyl acetate/hexane mixture (7:3) to give a very good yield of an oil which forms a unitary spot at $R_f=0.65$ in a thin layer chromatographic analysis carried out with the same eluent.

Chemical-physical characteristics: $[\alpha]_D^{20}=+70.5°$ (C=1% in $CHCl_3$); λ_{max} (MeOH)=235 mμ (ε=18,750); IR (nujol) cm^{-1}: 3480 (11 O—H and 17 O—H), 1740—1725 (C=O ester and 20-keto), 1665, 1625, 892 (C=O 3-keto $\Delta^{1,4}$); NMR ($CDCl_3$) δ: 4.93 (s, 2H, C—21 CH_2), 5.15—5.65 (m, 4H, olefinic protons in chain) 6.13 (d, $J_{2,4}=1$ cps, 1H, C—4 C—H), 6.32 (dd, $J_{2,4}=1$ cps, $J_{1,2}=10$ cps, 1H, C—2 C—H), 7.27 (d, $J_{1,2}=10$ cps, 1H, C—1 C—H).

The results of the analysis are in accordance with the empirical formula $C_{40}H_{59}FO_6$.

Example 3

9α-fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione 21-octadeca-cis-9,cis-12,cis-15-trienoate (Dexamethasone 21-linolenate).

The dexamethasone 21-mesylate (11.5 g.; 24.5 millimoles) prepared as described in Example 1 was added, in a nitrogen atmosphere, to a stirred slurry of potassium octadeca-cis-9,cis-12, cis-15-trienoate (7.76 g.; 24.5 millimoles) in 70 ml. DMF. After stirring for 1.5 hours at 50°C. and evaporating the solvent *in vacuo* at the same temperature, the residue was washed by slurrying it into water and was then redissolved in methylene chloride, dried and the solvent evaporated. The residue was purified by chromatography on an inactivated (10% water) silica gel column (490 g.) by using an ethyl acetate/hexane mixture (7:3) to give a very good yield of an oil which forms a unitary spot at $R_f=0.65$ in a thin layer chromatographic analysis carried out with the same eluent.

Chemical-physical characteristics: $[\alpha]_D^{20}=+64.1°$ (C=1% in $CHCl_3$); λ_{max} (MeOH)=240 mμ (ε=16,700); IR (nujol) cm^{-1}: 3520 (11 O—H and 17 O—H), 1745—1720 (C=O ester and 20-keto), 1665, 1630, 892 (C=O 3 keto $\Delta^{1,4}$); NMR ($CDCl_3$): δ=4,92 (s, 2H, C—21 CH_2), 5.17—5.62 (m, 6H, olefinic protons in chain), 6.14 (d, $J_{2,4}=1$ cps, 1H, C—4 C—H) 6.35 (dd, $J_{2,4}=1$ cps, $J_{1,2}=10$ cps, 1H, C—2 C—H), 7.25 (d, $J_{1,2}=10$ cps, 1H, C—1 C—H).

The results of the analysis are in accordance with the empirical formula $C_{40}H_{57}FO_6$.

Example 4

9α-fluoro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 21-octadeca-cis-9, cis-12-dienoate (Betamethasone 21-linoleate).

9α - fluoro - 11β,17,21 - trihydroxy - 16β - methyl - pregna - 1,4 - diene-3,20 - dione (10 g., 25.5 millimoles) was treated with methane sulfonyl chloride (3 ml.; 48.5 millimoles) in the same conditions as described in Example 1 to give 11.75 g. (98% of theoretical yield) of betamethasone 21-mesylate, m.p. 180—182°C. (dec.).

The above mesylate intermediate was added in nitrogen atmosphere to a stirred slurry of potassium octadeca-cis-9, cis-12-dienoate (7,96 g.; 25 millimoles) in 70 ml. DMF. After stirring for 1.5 hours at 50°C. and evaporating the DMF at the same temperature, the resulting residue was washed by slurrying it into water and was then redissolved in methylene chloride, dried and the solvent evaporated. The residue was purified by chromatography on an inactivated (10% water) silica gel column, by using an ethyl acetate/hexane mixture (7:3) to give a very good yield of an oil which forms a unitary spot at R_f=0.65 in a thin layer chromatographic analysis carried out with the same eluent.

Chemical-physical characteristics: λ_{max} (MeOH)=238 mμ (ε=18.200); IR ($CHCl_3$)cm^{-1}: 3450 (11 O—H and 17 O—H). 1745—1720 (C=O ester and 20-keto), 1665, 1630, 890 (C=O 3-keto $\Delta^{1,4}$); NMR ($CDCl_3$) δ: 4.92 (s, 2H, C—21 CH_2) 5,13—5,53 (m, 4H, olefinic protons in chain), 6,07 (d, $J_{2,4}$=1 cps, 1H, C—4 CH), 6,28 (dd, $J_{2,4}$=1 cps, $J_{1,2}$=10 cps, 1H, C—2 CH), 7.24 (d, $J_{1,2}$=10 cps, 1H, C—1 CH).

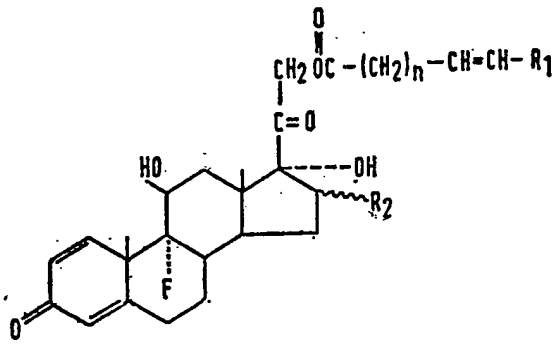
The results of the analysis are in accordance with the empirical formula $C_{41}H_{59}FO_6$.

It will be appreciated that other pregnane compounds according to the invention may be prepared by specific processes similar to those of the foregoing Examples, the necessary modifications to the reactants used and to variables such as temperature, being made.

WHAT WE CLAIM IS:—

1. A pregnene compound of the general formula:

(I)



wherein R_1 is an unsaturated or saturated aliphatic hydrocarbon group having from 8 to 14 carbon atoms, R_2 is an α-orientated or β-orientated methyl group, and n is a positive integer of from 3 to 7.

2. A pregnene compound as claimed in claim 1 wherein R_1 has either 8 or 14 carbon atoms and n has a value of either 3 or 7.

3. A pregnene compound as claimed in claim 2 wherein R_2 is an α-orientated methyl group.

4. A pregnene compound as claimed in claim 2 wherein R_2 is a β-orientated methyl group.

5. A pregnene compound as claimed in claim 3 or claim 4 wherein R_1 is an n-octyl group and n has a value of 7.

6. A pregnene compound as claimed in claim 3 or claim 4 wherein R_1 is a group of the formula $—CH_2—CH=CH—(CH_2)_4—CH_3$ and n has a value of 7.

7. A pregnene compound as claimed in claim 3 or claim 4 wherein R_1 is a group of the formula $—CH_2—CH=CH—CH_2—CH=CH—CH_2—CH_3$ and n has a value of 7.

GB1292785

Patent number: GB1292785

Publication date: 1972-10-11

Inventor:

Applicant:

Classification:

- international:

- european:

Application number: GBD1292785 19710419

Priority number(s): IT19700031143 19701017

Also published as:

FR2112302 (A1)

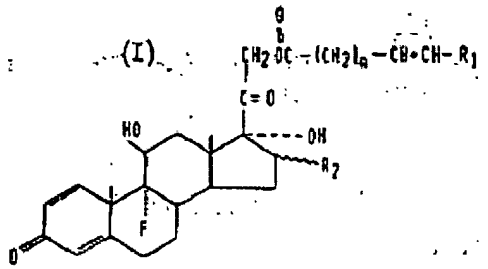
DE2113163 (A1)

BE764130 (A)

IT1043956 (B)

Abstract of **GB1292785**

1292785 Esters of dexamethasone and beta-methasone ISF SpA 19 April 1971 [17 Oct 1970] 22811/71 Heading C2U Novel steroids of the formula (wherein R 1 is a saturated or unsaturated hydro- carbon group of 8-14 carbon atoms and n is 3, 4, 5, 6 or 7) are prepared by reacting beta- W ethasone or dexamethasone, or an ester there- of e.g. a 21-mesylate, with the appropriate acid R 1 CH = CH(CH 2) n CO 2 H or a salt thereof. Suitable acids include oleic, linoleic, linolenic and arachidonic acids. Dexamethasone and betamethasone 21-mesylates are prepared from the free 21-ols and mesyl chloride. The novel steroids are stated to possess anti- inflammatory activity, and they may be made up into pharmaceutical compositions with suitable carriers.



GB1292785

Description of **GB1292785**

(54) DERIVATIVES OF DEXA- AND BETA-METHASONE,
THEIR PRODUCTION AND USE
(71)We, I.S.F. S.p.A., an Italian Body Corporate of Via Calatafimi5-9,
Milan, Italy, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: -
The invention relates to novel pregnene compounds, to a method for their preparation and also to their pharmaceutical use. In accordancewith the invention the novel compounds are produced byesterifving the alcoholic group in the 21-position of a corticoid with an unsaturated higher fatty acid having non-cumulative double bonds.

The novel compounds of the invention have high antiphlogistic, (i.e. anti-inflammatory) anti-exudative and antipruritic activities.

It is known that the antiphlogistic activity of a corticoid is substantially affected by the kind of acid radical bonded to the 21-position; furthermore, the lipophilic character of a steroid is enhanced by aliphatic high-molecular weight chains in the 21position.

It has now been found that the esters of the high molecular weight aliphatic chains obtained by. esterifying the alcoholic group of the 21-position in the steroid nucleus with certain unsaturated carboxylic acids, for instance, oleic acid, linoleic acid or arachidonic acid show new and unexpected features.

According to the invention, there are provided pregnene compounds of the general formula:
EMI1.1
whereinR@ is an unsaturated or saturated aliphatic hydrocarbon group having from S to 14 carbon atoms, for instance, either 8 carbon atoms or 14 carbon atoms,R2 is an a-orientated or P-orientated methyl group, and n is a positive integer of from 3 to 7, preferably either 3 or 7.

When n has a value of 7, the substituent R4 is preferably an n-octyl group, a group of the formula -CH2-CH=CH-(CH2)4-CH3 or a group of the formula ~~ -CWCH = CII-CH2-CH = CH-CHCW.

In the case where n has a value of 3, the substituent R, is preferably a group of the formula --(CH,CH =CH)3(CW)4CH,.

The esters of the invention may be prepared by a process comprising reacting an unsaturated fatty acid or salt thereof (usually about an equimolar amount), the said fatty acid having the formula:
EMI2.1
wherein R1 and n are as defined above, with dexa-methasone or beta-methasone or a 21-ester thereof, the aforesaid methasone having the formula:
EMI2.2
wherein R2 is asdefined above.

The unsaturated fatty acid of the general formula (II) is preferably linoleic acid, oleic acid, arachidonic acid or linolenic acid. The methasone may be in the form of the2 1-mesylate.

The reaction is conveniently carried out in an aprotic solvent for example, dimethyl formamide, and is preferably effected at a temperature of100C. to 700C.

cspeciallySOC. In order to avoid oxidation of the double bonds in the unsaturated fatty acid, the reaction should preferably be carried out in an inert atmosphere (e.g.

nitrogen).

The esters of the invention are oily or soft fatty materials, whereas the esters prepared from saturated acids having the same number of carbon atoms (e.g. palmitic acid) are crystalline solids. This feature may

have desirable effects on both the surface penetration and the extension in time ("delay effect") of the drug. A surface penetration may occur in the absence of the usual carriers although the latter are usually desirably present, mostly for facilitating the administration of the drug.

In connection with the "delay effect" referred to above, it has been found that thecortsone-related moiety of the esters according to the invention is slowly and gradually released by hydrolysis of the ester bond, thereby permitting distribution andc ;tension of the thcrapcutical action over a suitable period of time. The above features, in conjunction with the absence of side-effects, which results from the lack of systematic action, render the esters according to the invention to show a relatively high topical anti-phlogistic action.

The esters of this invention may, for theirtherapcutic function, be administered alone or in admixture with inert and pharmaceutically acceptable diluents or carriers and/or other biologically active compounds.

Embodiments of the invention will now be described by way of example in the following Examples:
Example 1: 9α-fluoro-11ss,17,21-trihydroxy-16α-methyl-pregna-1,4-diene-3,20-dione 21-octadec-cis-9-enoate (Dexamethasone 21-oleate)
To a stirred solution of9α-fluoro-11ss,17,21-trihydroxy-16α-methyl-pregna-1,4- diene-3,20-dione (10 g.; 25.5 millimoles) in 20 ml. pyridine and 12 ml. acetone at- 10CC. a a cold solution of methane sulfonyl chloride (3 ml.; 38.5 millimoles) in S ml.

acetonewas added dropwise. The addition was completed within about 3 hours, and the mixture was then left standing in the cold for a further 1.5 hours after which 200 ml. cold water were added. The resulting precipitate as separated by filtration and washed with water to give 11.5 g. (96% of theoretical yield) of dexamethasone21 - mesylate, m.p. 208-210 C. (dec.).

The above mesylate (intermediate) was added, in a nitrogen atmosphere, to a stirred slurry of potassium octadec-cis-9-enoate (7.85 g.; 24.5 millimoles) in 70 ml.

dimethyl formamide (DMF). After stirring for 1.5 hours at 500C. and evaporating the DMF in vacuo at the same temperature, the residue as washed by slurrying it into water and then was redissolved in methylene chloride, dried and the solvent evaporated. The residue was purified by chromatography on an inactivated (10% water) silica gel column(550 g.), by using an ethylacetatejhexane mixture (7:3) to give a very good yield of an oil which forms a unitary spot at Rf=0.65 in a thin layer chromatographic analysis carried out with the same eluent.

Chemical-physical characteristics:[α]D20=+84.9 (C=1% in CHCl3);#max(MeOH)=240 m@ (#=14.100); IR (*nujol) cm-1: 3470 (11 O-H and 17 O-H),1735-1715 (C=O ester and 20-keto), 1660,1620, 890 (C=O 3-keto#1.1);
NMR (CDCl3)#:: 4.93 (s, 2H, <RTI 21 CH2),5.10-5.65 (m, 2H, olefinic protons in chain), 6.10 (d, J2,4=1 cps, 1H, C-4C-H), 6.32 (dd,J24=1 cps,J,?=10 cps, 1H,C-2 C-H), 7.24 (d, J1.2=10 cps, 1H,C-1 C-H).
("Nujol" is a Registered Trade Mark).

The results of the analysis are in accordance with empirical formulaC40H0@FO6.

Example 2: 9α-fluoro-11ss,17,21-trihydroxy-16α-methyl-pregna-1,4-diene-3,20-dione 21-octadeca-cis-9, cis-12-dienoate (Dexamethasone 21-linoleate)
The dexamethasone 21-mesylate (11.5 g.; 24.5 millimoles) prepared as described in Example 1 was added in a nitrogen atmosphere to a stirred slurry of potassium actadeca-cis-9, cis, 12-dienoate (7.81 g.; 24.5 millimoles) in 70 ml. DMF. After stirring for 1.5 hours at 500C. and evaporating the solvent in vacuo at the same temperature, the residue was washed by slurrying it into water and was then redissolved in methylene chloride, dried and the solvent evaporated.The residue was purified by chromatography on an inactivated(10 water) silica gel column (470 g.) by using an ethyl acetate/hexane mixture(7: 3) to give a very good yield of an oil which forms a unitary spot at Rf=0.65 in a thin layer chromatographic analysis carriedotit with the same eluent.

Chemical-physical characteristics:[α]D20=+70.5 (C=1% in CHCl3);#max (MeOH)=235 mBt (#=18,750); IR (nujol)cml: 3480 (11 O-H and 17 O-H), 1740-1725 (C=O ester and 20-keto), 1665, 1625, 892 (C=O 3-ketoA14); NMR(CDCl?,) #: 4.93 (s, 2H,S21 CH2),5.15-5.65 (m, 4H, olefinic protons in chain) 6.13 (d, J2,4=1 cps, 1H, C-4C-H), 6.32 (dd, J2,4=1 cps, J1,2=10 cps, 1H,C-2 C-H), 7.27 (d, J1,2=10 cps, 1H,C-1 C-H).

The results of the analysis are in accordance with the empirical formula C40H59FO6.

Example 3 9α-fluoro-11ss,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione 21-octadeca-cis-9,cis-12,cis-15-trienoate (Dexamethasone 21-linolenate).

Thedexamethasone 21-mesylate (11.5 g.; 24.5 millimoles) prepared as described in Example 1 was added, in a nitrogen atmosphere, to a stirred slurry of potassiumoctadec3-cis-9,cis-l2, cis-15-trienoate (7.76 g.; 24.5 millimoles) in 70 ml. DMF. After stirring for 1.5 hours at 50 C. and evaporating the solvent in vacuo at the same temperature, the residue was washed by slurrying it into water and was then redissolved in methylene chloride, dried and the solvent evaporated. The residue was purified by chromatography on an inactivated (10% water) silica gel column (490 g.) by using an ethyl acetate/hexane mixture (7:3) to give a very good yield of an oil which forms a unitary spot at Rf=0.65 in a thin layer chromatographic analysis carried out with the same eluent.

Chemical-physical characteristics:[α]D20=+64.1 (C=1% in CHCl3);#max (MeOH)=240 m (#=16,700); IR (nujol) cm-1: 3520 (11 O-H and 17 O-H),1745-1720 (C=O ester and20-keto), 1665, 1630, 892 (C=O 3 keto#1,4); NMR (CDCl3):#=4,92 (s, 2H, C-21 CH2), 5.17-5.62 (m, 6H, olefinic protons in chain), 6.14 (d, J2,4=1 cps, 1H,C t C H) 6.35 (dd,J,4 1 cps, J1,2=10 cps,1H, C-2 C-H), 7.25 (d, J1,2=10 cps, 1H, C-1 C-H).

The results of the analysis are in accordance with the empirical formula C40H57FO6.

Example 4 9α-fluoro-11ss,17,21-trihydroxy-16ss-methylpregna-1,4-diene-3,20-dione 21-octadeca-cis-9, cis-12-dienoate (Betamethasone 21-linoleate).

9α - fluoro - 11ss,17,21 - trihydroxy - 16ss - methyl - pregna - 1,4 - diene- 3,20 - dione (10 g., 25.5 millimoles) was treated with methane sulfonyl chloride (3 ml.; 48.5 millimoles) in the same conditions as described in Example 1 to give 11.75 g. (98 of theoretical yield) of betamethasone 21-mesylate, m.p. 180-182 C.

(dec.).

The above mesylate intermediate was added in nitrogen atmosphere to a stirred slurry of potassium octadeca-cis-9, cis-12-dienoate (7,96 g.; 25 millimoles) in 70 ml.

DMF. After stirring for 1.5 hours at 500C. and evaporating the DMF at the same temperature, the resulting residue waswashed by slurrying it into water and was then redissolved in methylene chloride, dried and the solvent evaporated. The residue was purified by chromatography on an inactivated (10% water) silica gel column, by using an ethyl acetate/hexane mixture (7:3) to give a very good yield of an oil which forms a unitary spot at Rf=0.65 in a thin layer chromatographic analysis carried out with the same eluent.

Chemical-physical characteristics:#max (MeOH)=238 m (#=18.200); IR (CHCl3)cm-1: 3450 (11 O-H and 17 O-H). 1745-1720 (C=O ester and 20keto), 1665, 1630, 890 (C=O 3-keto#1,4); NMR (CDCl3)#: 4.92 (s, 2H, C-21 CH2) 5,13-5,53 (m, 4H, olefinic protons in chain), 6,07 (d, J2,4=1 cps, 1H, C-4 CH), 6,28 (dd, J2,4=1 cps,J1 =10 cps, 1H,C-2 CH8, 7.24 (d, J1,2=10 cps, 1H,C-I CH).

The results of the analysis are in accordance with the empirical formula C40H57FO6.

It will be appreciated that other pregnane compounds according to the invention may be prepared by specific processes similar to those of the foregoing Examples, the neccssary modifications to the reactants used and to variables such as temperature, being made.

WHAT WE CLAIMIS:-

1. A pregnene compound of the general formula:

EMI4.1

wherein R1 is an unsaturated or saturated aliphatic hydrocarbon group having from 8 to 14 carbon atoms,

R2 is anα-orientated or ss-orientated methyl group, and n is a positive integer of from 3 to 7.

2. A pregnene compound as claimed in claim 1 wherein R1 has either 8 or 14 carbon atoms and n has a value of either 3 or 7.

3. A pregnene compound as claimed in claim 2 wherein R2 is anα-orientated methyl group.

4. A pregnene compound as claimed in claim 2 wherein R2 is a ss-orientated methyl group.

5. A pregnene compound as claimed in claim 3 or claim 4 wherein R, is an n-octyl group andn has a value of 7.

6. A pregnene compound as claimed in claim 3 or claim 4 wherein R1 is a group of the formula -CH2-CH=CH-(CH2)4-CH3 and n has a value of 7.

7. A pregnene compound as claimed in claim 3 or claim 4 wherein R1 is a group of the formula -CH2-CH=CH-CH2-CH=CH-CH2-CH3 and n has a value of 7.

WARNING end of DESC field may overlap start of CLMS **.

GB1292785

Claims of **GB1292785**

WARNING start of CLMS field may overlap end of DESC **.

Example 4 9α-fluoro-11ss,17,21-trihydroxy-16ss-methylpregna-1,4-diene-3,20-dione 21-octadeca-cis-9, cis-12-dienoate (Betamethasone 21-linoleate).

9α - fluoro - 11ss,17,21 - trihydroxy - 16ss - methyl - pregna - 1,4 - diene- 3,20 - dione (10 g., 25.5 millimoles) was treated with methane sulfonyl chloride (3 ml.; 48.5 millimoles) in the same conditions as described in Example 1 to give 11.75 g. (98 of theoretical yield) of betamethasone 21-mesylate, m.p. 180-182 C.

(dec.).

The above mesylate intermediate was added in nitrogen atmosphere to a stirred slurry of potassium octadeca-cis-9, cis-12-dienoate (7,96 g.; 25 millimoles) in 70 ml.

DMF. After stirring for 1.5 hours at 500C. and evaporating the DMF at the same temperature, the resulting residue waswashed by slurrying it into water and was then redissolved in methylene chloride, dried and the solvent evaporated. The residue was purified by chromatography on an inactivated (10% water) silica gel column, by using an ethyl acetate/hexane mixture (7:3) to give a very good yield of an oil which forms a unitary spot at Rf=0.65 in a thin layer chromatographic analysis carried out with the same eluent.

Chemical-physical characteristics:#max (MeOH)=238 m (#=18.200); IR (CHCl3)cm-1: 3450 (11 O-H and 17 O-H). 1745-1720 (C=O ester and 20keto), 1665, 1630, 890 (C=O 3-keto#1,4); NMR (CDCl3)#: 4.92 (s, 2H, C-21
CH2) 5,13-5,53 (m, 4H, olefinic protons in chain), 6,07 (d, J2,4=1 cps, 1H, C-4
CH), 6,28 (dd, J2,4=1 cps,J1 =10 cps, 1H,C-2 CH8, 7.24 (d, J1,2=10 cps, 1H,C-I CH).

The results of the analysis are in accordance with the empirical formula C40H57FO6.

It will be appreciated that other pregnane compounds according to the invention may be prepared by specific processes similar to those of the foregoing Examples, the neccssary modifications to the reactants used and to variables such as temperature, being made.

WHAT WE CLAIMIS:-

1. A pregnene compound of the general formula:
EMI4.1
wherein R1 is an unsaturated or saturated aliphatic hydrocarbon group having from 8 to 14 carbon atoms, R2 is anα-orientated or ss-orientated methyl group, and n is a positive integer of from 3 to 7.

2. A pregnene compound as claimed in claim 1 wherein R1 has either 8 or 14 carbon atoms and n has a value of either 3 or 7.

3. A pregnene compound as claimed in claim 2 wherein R2 is anα-orientated methyl group.

4. A pregnene compound as claimed in claim 2 wherein R2 is a ss-orientated methyl group.

5. A pregnene compound as claimed in claim 3 or claim 4 wherein R, is an n-octyl group andn has a value of 7.

6. A pregnene compound as claimed in claim 3 or claim 4 wherein R1 is a group of the formula -CH2-CH=CH-(CH2)4-CH3 and n has a value of 7.

7. A pregnene compound as claimed in claim 3 or claim 4 wherein R1 is a group of the formula -CH2-CH=CH-CH2-CH=CH-CH2-CH3 and n has a value of 7.
